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INNOVATIONS FOR LIVING®

VIA E-MAIL AND REGULAR MAIL

May 22, 2009

Dr. Ruth Lunn
National Toxicology Program
National Institute of Environmental
Health Sciences
Building 4401, EC/3118
79 Alexander Drive
Research triangle Park, NC 27709

Re: Comments from Owens Corning Corporation, John G. Hadley, Ph.D.

Dear Dr. Lunn:

I appreciate the opportunity to comment on the Draft Background Document for Glass Wool Fibers. By way of background, I have been involved in fiber health effects research for over 20 years, and I was co-study director on the chronic inhalation studies of insulation glass wools MMVF 10 and MMVF11. I have also co-authored numerous papers on the role of durability on the health effects of glass fibers (Appendix A). My comments focus on two major topics:

1. Historic perspective on the request for delisting "glass wool (respirable size)" by the NTP.
2. Supplemental information regarding the role of fiber durability that is relevant to insulation glass wools and should be included in section 5.2 of the Draft Background Document.

BACKGROUND: THE BASIS FOR DELISTING GLASS WOOL (RESPIRABLE SIZE)

The delisting of "glass wool (respirable size)" stems from the (October 16, 2001) International Agency for Research on Cancer ("IARC") decision to change its 1988 classification of "glass wool" as a Group 2B material. In 2001 IARC moved to individual classifications of "insulation glass wool" as a Group 3 and "special-purpose fibers" as Group 2B. The reclassification was premised on the recognition by IARC that there were differences in the science for the two families of glass fibers (insulation glass wool and special-purpose glass fibers) that made up its 1988 category called "glass wool." IARC's reclassification concluded that the human data for glass wool (both insulation glass wool and special-purpose glass fibers) remained "inadequate," but that the animal data needed to be interpreted differently for each of the subgroups. IARC

determined that the animal data was "limited" for the insulation glass wools but was "sufficient" for special-purpose glass fibers. NAIMA's delisting nomination applies only to glass wool insulation.

IARC also determined that mechanistic considerations regarding fiber durability provided additional information supporting its clarification.

Human Data

IARC's 2001 evaluation of the epidemiological data reached the same conclusion that it had reached in its original evaluation in 1988. It found that the human data was "inadequate" for the entire category of "glass wool." As in 1988, the available human data was extensive. In fact, the largest of the studies examined in 1988 had continued and updated findings were available to IARC for its 2001 assessment. IARC commented on the scope and quality of the epidemiological data available to it in 2001 in its press release announcing its findings:

> These [Synthetic Vitreous Fibers or SVF] products, including glass wool . . . have been in use for decades and have been extensively studied to establish whether fibres that are released during manufacture, use, or removal of these products present a risk of cancer when inhaled. Epidemiologic studies published during the 15 years since the previous IARC Monographs review of these fibres in 1988 provide no evidence of increased risks of lung cancer or of mesothelioma (cancer of the lining of the body cavities) from occupational exposures during manufacture of these materials, and inadequate evidence overall of any cancer risk.[1]

Animal Data

In 2001, IARC changed its assessment of the animal data for insulation glass wool by evaluating it as "limited." This was due to (1) the availability of well-conducted chronic inhalation studies in two species conducted at or above the MTD, which showed no evidence of either fibrosis or significant tumor induction with the glass wool insulations; (2) the growing consensus regarding the relevance of route of administration in assessing the hazard of fibers; and (3) extensive data on the critical role of fiber durability or biopersistence.

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[1] A copy of the IARC October 24, 2001 press release is attached, and is available at: http://www.iarc.fr/en/media-centre/pr/2001/pr137.html (last visited May 20, 2009).

THE CHRONIC INHALATION STUDIES

An early report on the multidose rat inhalation study (Hesterberg, *et al.*, 1993)[2] was evaluated by NTP prior to the listing of glass fibers in the 7th RoC. At that time, NTP raised two questions regarding the study. The first related to the adequacy of the doses used, and the second was the relatively high background tumor rate in the concurrent control group. Since the original NTP listing, significant new research has been published that directly addresses these two questions.

Regarding doses used, Hesterberg, *et al.* (1996)[3] reported on subchronic studies assessing lung toxicity and lung particle clearance to estimate the MTD for a glass wool insulation chronic inhalation study in rats. The authors reported that the dose used in the chronic study was the highest dose appropriate for the rat inhalation study. Additionally, Tran, *et al.* (1996)[4] found "[e]vidence of overload, dissolution and breakage of MMVF 10 fibres in the RCC chronic inhalation study," further supporting the adequacy of the dosing in the chronic study.

On the issue of background tumor rates, subsequent to the original NTP listing, Rossiter and Chase published "Statistical Analysis of Results of Carcinogenicity Studies of Synthetic Vitreous Fibres at Research and Consulting Company, Geneva."[5] That study concludes:

> No insulation wool (glass, stone or slag) exposure group had a lung tumour rate that differed statistically significantly from the tumour rate for the respective concurrent control groups, sham-exposed to filtered air. There was no significant difference in the total tumour rates between the four insulation wool groups and the control animals, and no significant dose-response relation above the respective sham-exposed control tumour rates.[6]

Furthermore, Hesterberg and Chase compared the background lung tumor rate in the chronic rat study of MMVF 10 and 11 to the comparable rate in NTP bioassays:

> [I]n the NTP historical controls from inhalation studies, the route of exposure used for the fiber glass study is 4.3% (13/398). Clearly, the lung tumor incidence

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[2] T.W. Hesterberg, W.C. Miiller, E.E. McConnell, J. Chevalier, J.G. Hadley, D.M. Bernstein, P. Thevenaz, and R. Anderson, "Chronic Inhalation Toxicity of Size-Separated Glass Fibers in Fischer 344 Rats," *Fundamental and Applied Toxicology* 20, 464-476 (1993).

[3] T.W. Hesterberg, E.E. McConnell, W.C. Miiller, J. Chevalier, J. Everitt, P. Thevenaz, H. Fleissner, and G. Oberdorster, "Use of Lung Toxicity and Lung Particle Clearance to Estimate the Maximum Tolerated Dose (MTD) for a Fiber Glass Chronic Inhalation Study in the Rat," *Fundamental and Applied Toxicology* 32, 31-44 (1996).

[4] C.L. Tran, A.D. Jones and K. Donaldson, "Evidence of overload, dissolution and breakage of MMVF10 fibres in the RCC chronic inhalation study," *Exp. Toxic Pathol*: 48: 500-504 (1996).

[5] C.E. Rossiter and J.R .Chase, "Statistical Analysis of Results of Carcinogenicity Studies of Synthetic Vitreous Fibres at Research and Consulting Company, Geneva," *Ann. Occup. Hyg.*, Vol. 39, No. 5, pp. 759-769 (1995).

[6] *Ibid.*, p. 759.

> of 3.1% observed in the concurrent controls in the fiber glass study is consistent with the most recent NTP historical controls.[7]

The IARC Working Group acknowledged the significance and protocol improvements of these new inhalation studies. Specifically referring to these studies, IARC stated:

> More recent inhalation studies in rodents have addressed the technological limitations of the earlier studies using test fibres prepared by new size-separation methods. Such fibres are respirable by rats and long enough to be biologically active, with nominal dimensions of 1 x 20 [microns]. An aerosolization system has been designed to create uniform, high concentrations of airborne fibres without destroying the biologically important long-thin fibre geometry. In the chronic inhalation studies of MMVF's reviewed in section 3, the Working Group has clearly noted those studies that they considered to be 'well-conducted long-term inhalation studies' which meet the criteria summarized above.[8]

In addition to these studies on glass wools, "well conducted long term inhalation studies" were reported for rock and slag wools, again showing no lung or pleural tumors.

The fundamental importance of these findings is that for each of the three major types of insulation wools – glass, rock and slag – the Working Group found the overall evidence of carcinogenicity in animals to be "limited" although there were reports of tumor formation with each of the insulation wools following intraperitoneal injection. The Working Group summarized the glass wool insulation data as follows:

> **Insulation glass wool (animal evidence "limited")**
>
> Insulation glass wools were tested in well-designed, long-term inhalation studies in rats and hamsters. No significant increase in lung tumours and no mesotheliomas were observed in rats and no lung tumours or mesotheliomas were observed in hamsters exposed to insulation glass wool. Two different asbestos types used as positive controls produced increases in lung tumours and mesotheliomas.
>
> Two insulation glass wools that produced no increase in tumours when administered by inhalation did induce mesotheliomas when injected at high doses (approximately 10^9 fibers) into the peritoneal cavity of rats.[9]

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[7] T.W. Hesterberg, G. R. Chase, "Commentary on Fibrous Glass and Lung Cancer," *American Journal of Industrial Medicine,* 30:111-112 (1996), p. 111.
[8] IARC Monograph 81, p. 37.
[9] The same conclusions were stated for rock (stone) wool and for slag wool. IARC Monograph 81, p. 332.

THE CRITICAL ROLE OF FIBER DURABILITY OR BIOPERSISTENCE

The now well-established role of fiber biopersistence in the potential biological activity of fibers also played an important role when IARC evaluated the animal data with respect to insulation glass wool. As noted by IARC:

> Increasing emphasis has been placed on clearance and retention of MMVFs in discussing the mechanistic data in risk assessment for adverse health effects induced by fibres (McClellan, 1977). This is partly because the biopersistence of fibres has been shown to play an important role in the effects on health of man-made and other mineral fibres.[10]

This recognition by IARC is also consistent with the 2000 NRC report:

> The potential hazards posed by a given MVF is directly related to its ability to persist in the lung long enough to cause chronic disease.[11]

IDENTIFICATION AND SUPPLEMENTAL INFORMATION RELEVANT TO INSULATION GLASS WOOLS IN SECTION 5.2 REGARDING THE ROLE OF FIBER DURABILITY

Section 5.2.2 of the Draft Background Document does not include important papers which provide data showing that for glass fibers, the relation between glass composition and *in vitro* dissolution rate has been extensively studied and that the composition can provide accurate estimates of the dissolution rate. For example, Eastes, *et al.* (2000),[12] provided data on 62 glass compositions and presented a model for calculating K_{dis} from compositions (Fig 3). The adjusted value for R^2 is 0.955 for this sample and the 95% confidence interval includes unity.

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[10] IARC Monograph 81, p. 255.

[11] National Research Council, *Review of the U.S. Navy's Exposure Standard for Manufactured Vitreous Fibers* (2000), p. 33.

[12] Eastes, W., Potter, R.M., and Hadley, J.G., "Estimating In Vitro Glass Fiber Dissolution Rate from Composition," *Inhalation Toxicology* 12:269-280 (2000).

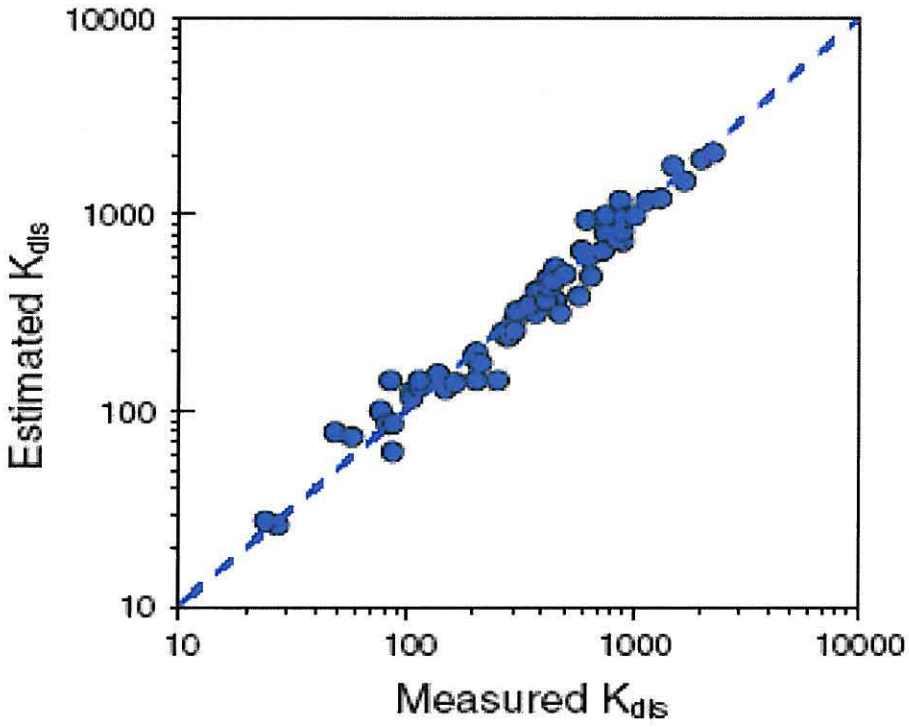
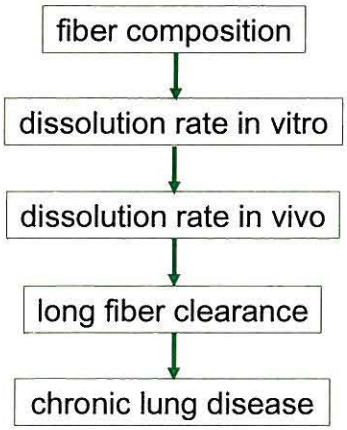


Fig. 3. Dissolution rate constant K_{dls} calculated from fiber composition compared to measured value. The confidence interval on the least squares slope includes unity Eastes et al., 2000a.

These data were part of a series of papers which provide an experimental validation of the four steps linking fiber composition to chronic lung disease shown in the figure below. The following paragraphs discuss the evidence for these links in the order shown below.



FIBER COMPOSITION PREDICTS DISSOLUTION RATE IN VITRO

A reasonable estimate of the in-vitro dissolution rate of synthetic vitreous fibers can be calculated for a range of borosilicate glasses with dissolution rates varying over a factor of 100,000 based on the linear relationship established between the logarithm of the dissolution rate and the oxide composition in weight percent.[13]

DISSOLUTION RATE IN VITRO PREDICTS DISSOLUTION RATE IN VIVO

In an intratracheal instillation study of 9 borosilicate fibers with dissolution rates ranging from 2 to 600 ng/cm^2/hr at pH 7.4, the diameter of long fibers (>20microns) recovered from the animals decreased steadily with the time after instillation; the rates of decrease were the same rates as which they dissolved in-vitro.[14]

Reasonably good agreement (R^2 = 0.7) between dissolution rates calculated from *in-vivo* data and *in-vitro* rates measured at pH 7.4 were also found for 26 synthetic vitreous fibers of diverse composition.[15]

DISSOLUTION RATE IN VIVO PREDICTS LONG FIBER CLEARANCE

Long fiber clearance data of 2 borosilicate glass wools, 2 traditional stone wools and crocidolite from rats after 5 days inhalation agreed well with predicted clearance data calculated assuming uniform dissolution at the dissolution rates measured *in vitro* at pH 7.4.[16]

LONG FIBER CLEARANCE PREDICTS CHRONIC LUNG DISEASE

A model with no adjustable parameters for the incidence of lung tumors and fibrosis in rats exposed to fibers by inhalation or intraperitoneal injection successfully predicted this incidence to within approximately the precision of the incidence measurement. The model is based on the concept that the incidence of disease depends solely on the lung residence time of long fibers, which can be calculated from the dissolution rates of the fibers measured *in vitro*.[17] This last Eastes, *et al.* paper is particularly important as it is cited repeatedly by Berry (1999) as discussed on page 208 of the Daft Background Document.

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[13] *Ibid.*, p. 276.
[14] Eastes, W., Morris, K.J., Launder, K.A., Collier, C.G., Davis, J.A., Mattson, S.M., Hadley, J.G., "Dissolution of Glass Fibers in the Rat Lung Following Intratracheal Instillation," *Inhalation Toxicology*, 7:197-213 (1995).
[15] Eastes, W., Potter, R.M., and Hadley, J.G., "Estimation of Dissolution Rate from In Vivo Studies of Synthetic Vitreous Fibers," *Inhalation Toxicology*, 12:1037-1054 (2000).
[16] Eastes, W., Hadley, J.G., "Dissolution of Fibers Inhaled by Rats," *Inhalation Toxicology*, 7:179-196 (1995).
[17] Eastes, W., Hadley. J.G, "A Mathematical Model of Fiber Carcinogenicity and Fibrosis in Inhalation and Intraperitoneal Experiments in Rats," *Inhalation Toxicology*, 8:323-343 (1996).

None of the above Eastes, *et al.* papers, as well as a number of others (*see* Maxim, *et al.* (2006)[18] for citations), are included in the Draft Background Document. The series of four papers by Eastes, *et al.*, should be added to the Draft Background Document so key data are available to the reader.

CONCERNS ABOUT BIOSOLUBLE FIBERS

In addition to the omissions above, there are several frequently mentioned concerns regarding the safety of biosoluble fibers which are not identified or discussed in the Draft Background Document. The first is the potential for systemic toxicity associated with inhalation of soluble fibers, and the second is that with daily exposure to fibers, even fibers which dissolve rapidly will be immediately replaced with newly arriving fibers.

Both of these questions are addressed specifically in Maxim, *et al.* (2006),[19] so only a brief summary will be made here. Potential systemic toxicity should not be a concern as seen by simply considering the mass of an inhaled fiber. For example, at 1 f/cc with the fibers being 1 micron in diameter and 20 microns long, the mass of the 1 million fibers in a cubic meter of air would be 40 micrograms. For the 10 cubic meters inhaled during a workday, the total inhaled mass would be 400 micrograms. If 25% of the fibers were deposited in the lung, the total mass would be 100 micrograms per day. Contrast this to ACGIH TLV values for the various oxides (ranging from 2-10 mg/c^3 for the common oxides in insulation glass wool fibers), and it can be determined that the inhaled fibers would contribute less than 1% of the daily amount inhaled at the TLV.

The second question regarding the effect of the constant replacement of fibers with newly deposited fibers in the lungs also is not a realistic concern due to the anatomy of the human lung. Using the example above, one would have 2.5 million fibers deposited in the lower lung in one work day. As the human lung contains about 500 million alveoli, it would take over 6 months to achieve an average of 1 fiber per alveoli. However, if one considers that it is the long (>20 microns) fibers that are of most concern, and if they represent 25% of the inhaled fibers, there would be about 625,000 fibers per work day spread among the 500 million alveoli. In this case, it would take over two years to achieve an average of 1 long fiber per alveoli. Since insulation wool fibers dissolve in a matter of weeks or months, the concept of constant deposition and bioaccumulation of fibers in the alveoli is not correct.

In summary, the extensive database on the durability and biopersistence of insulation glass wool fibers is not presented in sufficient detail in the Draft Background Document. Given the importance of the topic, a more informative discussion is warranted.

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[18]Maxim, L. D., Hadley, J. G., Potter, R. M., and Niebo, R., "The role of fiber durability/biopersistence of silica-based synthetic vitreous fibers and their influence on toxicology," *Regulatory Toxicology and Pharmacology*, 46(1): 42-62, pp. 54-55 (2006).

[19] *Ibid.* at 54-55.

CONCLUSION

As summarized above, and discussed in more detail in the IARC Monograph, in ATSDR, and in many published papers (both before and after the IARC Monograph), the fibers used to manufacture glass wool insulation (MMVF 10 and 11) did not produce statistically significant lung tumors, mesotheliomas or fibrosis in well-conducted animal inhalation studies. These findings are consistent with the other relevant data showing glass wool insulation fibers have low durability and short biopersistence as measured in a variety of *in vivo* and *in vitro* studies. Moreover, a few questions identified by IARC concerning the interpretation of the MMVF 10 and 11 inhalation studies have been answered by studies published since the Monograph was published.

Sincerely

[Redacted]

John G. Hadley, Ph.D.
Director of Toxicology

Peer Reviewed Publications: Fiber Related

1. Maxim, L. D., Hadley, J. G., Potter, R. M., and Niebo, R., "The role of fiber durability/biopersistence of silica-based synthetic vitreous fibers and their influence on toxicology," *Regulatory Toxicology and Pharmacology,* 46(1): 42-62 (2006).

2. "Testing of Fibrous Particles: Short-Term Assays and Strategies, Report of an ILSI Risk Science Institute Working Group," *Inhalation Toxicology*, 17:497-537 (2005).

3. Maxim, L.D., Eastes, W., Hadley J.G., Carter, C.M., Reynolds, J.W., Niebo, R., "Fiber glass and rock/slag wool exposure of professional and do-it-yourself installers," *Regulatory Toxicology and Pharmacology*, 37: 28-44 (2003).

4. Fayerweather, W.E., Eastes, W., Cereghini, F., Hadley, J.G., "Quantitative Risk Assessment of Durable Glass Fibers," *Inhalation Toxicology*, 14:553-568 (2002).

5. Eastes, W., and Hadley, J.G., "Comment on "Long Man-Made Fibers and Lung Cancer Risk," *Regulatory Toxicology and Pharmacology*, 33: 268 (2001).

6. Eastes, W., Potter, R.M., and Hadley, J.G., "Estimating Rock and Slag Wool Fiber Dissolution Rates from Composition," *Inhalation Toxicology*, 12:1127-1139 (2000).

7. Eastes, W., Potter, R.M., and Hadley, J.G., "Estimation of Dissolution Rate from In Vivo studies of Synthetic Vitreous Fibers," *Inhalation Toxicology*, 12:1037-1054 (2000).

8. Eastes, W., Potter, R.M., and Hadley, J.G., "Estimating In Vitro Glass Fiber Dissolution Rate from Composition," *Inhalation Toxicology*, 12: 269-280 (2000).

9. Hesterberg, T.W, Chase, G., Axten, C., Miiller, W.C., Musselman, R.P., Kamstrup, O., Hadley, J. G., Morscheidt. C., Bernstein, D.M. and Thevenaz, P., "Biopersistence of Synthetic Vitreous Fibers and Amosite Asbestos in the Rat Lung following Inhalation," *Toxicology and Applied Pharmacology*, 151, 262-275 (1998).

10. Fayerweather, W., E., Bender, J.R., Hadley, J.G., Eastes, W., "Quantitative Risk Assessment for a Glass Fiber Insulation Product," *Regulatory Toxicology and Pharmacology*, 25: 103-120 (1997).

11. Eastes, W., Hadley, J.G. and Bender, J., "Assessing the Biological Activity of Fibers: Insights into the Role of Fiber Durability," *Australian/NZ Journal of Occupational Health and Safety*, 12(3): 381-385 (1996).

12. McConnell, E.E., Hesterberg, T, Chevalier, J., Thevenaz, P., Kotin, P., Mast, R., Musselman, R., Kamstrup, O., Hadley, J., "Results Of Life-Time Inhalation Studies of Glass, Mineral and Slag Wools and Refractory Ceramic Fibers in Rodents," *Australian/NZ Journal of Occupational Health and Safety*, 12(3): 327-332 (1996).

13. Eastes, W., Hadley. J.G, "A Mathematical Model of Fiber Carcinogenicity and Fibrosis in Inhalation and Intraperitoneal Experiments in Rats," *Inhalation Toxicology*, 8:323-343 (1996).

14. Eastes, W., Hadley, J.G., "Dissolution of Fibers Inhaled by Rats," *Inhalation Toxicology*, 7:179-196 (1995).

15. Eastes, W., Morris, K.J., Launder, K.A., Collier, C.G. , Davis, J.A., Mattson, S.M., Hadley, J.G., "Dissolution of Glass Fibers in the Rat Lung Following Intratracheal Instillation," *Inhalation Toxicology*, 7:197-213 (1995).

16. Eastes, W., Hadley, J.G., "Role of Fiber Dissolution in Biological Activity in Rats," *Regulatory Toxicology and Pharmacology*, 20: S104-S112 (1994).

17. Bender, J.R., Hadley, J.G., "Glass fiber Manufacturing and Fiber Safety: The Producers Perspective," *Environmental Health Perspectives*, 102: Supplement 5, 37-40 (1994).

18. Bernstein, D.B., Mast, R., Anderson, R., Hesterberg, T.W., Musselman, R., Kampstrup, O., Hadley, J.G., "An Experimental Approach to the Evaluation of the Biopersistence Of Respirable Synthetic Fibers and Minerals," *Environmental Health Perspectives*, 102 Supplement 5, 15-18 (1994).

19. Musselman, R.,P., Miiller, W. C., Eastes, W., Hadley, J.G., Kamstrup, O., Thevanez, P., and Hesterberg, T.W., "Biopersistence of Man-Made Vitreous Fibers and Crocidolite Fibers in Rat Lungs Following Short Term Exposure," *Environmental Health Perspectives*, 102 Supplement 5, 139-144 (1994).

20. Hesterberg, T.W., Miiller, W.C., McConnell, E.E., Chevalier, J.G. Hadley, J.G., Bernstein, D.M., Thevanez, P., and Anderson, R,, "Chronic Inhalation Toxicity of Size Separated Glass Fibers in Fischer 344 Rats," *Fundamental and Applied Toxicology*, 20:464-476 (1993).

21. Jacob, T.R., Hadley, J.G., Bender, J.R., Eastes, W., "Airborne Glass Fiber Concentrations during Manufacturing Operations Involving Glass Wool Insulation," *American Industrial Hygiene Association Journal*, 54: 320-326 (1993).

22. Jacob, T.R., Hadley, J.G., Bender, J.R., Eastes, W., "Airborne Glass Fiber Concentrations during Installation of Residential Insulation," *American Industrial Hygiene Association Journal*, 53:519-523 (1992).